

Individualized antithrombotic therapy in acute coronary syndrome: The role of thrombin pathway inhibition and aspirin

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ABSTRACT

Platelet-fibrin clot generation at the site of vascular injury in coronary arteries is a primary pathophysiologic event that leads to vascular occlusion and the subsequent clinical manifestations of acute coronary syndrome (ACS). Therefore, a strategy to optimally inhibit both platelet and coagulation pathways simultaneously — known as dual pathway inhibition (DPI) — has been proposed. In this strategy, when bleeding risk is acceptable, patients suffering from ACS are often treated with potent parenteral antiplatelet and anticoagulant therapies to facilitate efficient reperfusion and prevent reocclusion of coronary arteries. With the development of safer direct oral anticoagulants in recent years, a DPI strategy has been explored for the long-term management of patients with a history of ACS. It has been hypothesized that FXIa and FXIIa are essential for the amplification of thrombin generation beyond the initial burst of thrombin generated by tissue factor, and for the growth and stabilization of pathological clot, but not for normal hemostasis. In this scenario, potential oral agents include FXa (rivaroxaban, apixaban, edoxaban), FXIa (asundexian and milvexian), and FXIIa inhibitors. However, trials of full-dose FXa inhibitors added to an antiplatelet agent were associated with an unacceptable risk of bleeding. In patients with recent ACS, very low dose (2.5 mg bid) was associated with a significant reduction in efficacy endpoints compared to dual antiplatelet therapy and lower bleeding compared to 5 mg b.i.d. rivaroxaban dose. In patients with chronic atherosclerotic vascular disease, very low dose rivaroxaban plus aspirin compared to aspirin alone was associated with favorable net clinical benefits. Understanding the relative contributions of platelet and coagulation pathways to clot formation in an individual patient is likely critical to achieve a balance between anti-ischemic effects and bleeding risk. In this line, we discuss the importance of objectively measuring thrombogenicity and its potential role in personalizing DPI strategies in patients with ACS.

Key words: acute coronary syndrome, direct oral anticoagulants, dual pathway inhibition, platelets, thrombin, thrombogenicity

INTRODUCTION

Patients with acute coronary syndrome (ACS) can be regarded as “clot formers”. These patients have an inherent elevated risk for thrombosis. Generation of a thrombus at the site of vascular injury due to plaque rupture or erosion is a major cause of ACS. In this setting the thrombus mainly consists of aggregated platelets and a fibrin network. Because thrombus generation is dependent on the simultaneous activation of platelets and coagulation, a potentially ideal strategy is to inhibit both

pathways, known as dual pathway inhibition (DPI). When bleeding risk is acceptable, early after an index event or during coronary intervention, patients suffering from ACS are often treated with potent antiplatelet and anticoagulant therapies to maintain efficient reperfusion and prevent reocclusion of coronary arteries [1]. During long-term secondary management, earlier studies suggested that DPI with warfarin added to an antiplatelet agent was associated with a prohibitive bleeding risk [2]. Therefore, DPI was discouraged,

and the focus was largely confined to enhancing platelet inhibition with potent P2Y₁₂ receptor inhibitors (prasugrel and ticagrelor) along with aspirin.

Despite treatment with prasugrel and aspirin in the recent PROMETHEUS study of ACS patients who underwent percutaneous coronary intervention (PCI), the first-year major adverse cardiovascular events (MACE) rate was up to 23.3% in patients with a high thrombotic risk profile as defined in the 2020 European Society of Cardiology guidelines for non-ST-segment elevation (NSTEMI)-ACS [3, 4]. Similarly, in the ISAR REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial, patients with prior myocardial infarction (MI) and diabetes who were treated with ticagrelor or prasugrel had a first-year MACE rate of ~12% [5, 6]. The latter observations demonstrate a ceiling of benefit effect of the current strategy of adding a potent P2Y₁₂ receptor inhibitor to aspirin and a critical unmet need in preventing recurrent ischemic event occurrences in patients with ACS. With the development of direct oral anticoagulants (DOAC) that are safer than warfarin, a focus has been generated on potential long-term management of patients with a history of ACS by a DPI strategy.

However, trials of DPIs indicate that uniform treatment with a DOAC added to an antiplatelet agent is associated with an elevated risk of bleeding [7–9]. Guidelines and expert consensus recommend using bleeding risk scores based on demographic variables to triage patients for long-term DPI treatment [10, 11]. PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) or ARC-HBR (Academic Research Consortium for High Bleeding Risk) risk scores that can predict one-year major bleeding can be used to personalize therapy with DPIs [12, 13]. However, its implementation in the real world may be reduced due to lack of evidence from randomized trials. These risk scores do not include an assessment of the patients' inherent risk for thrombosis — hypercoagulability — measured by a reliable laboratory assay. Understanding the relative contribution of platelets and coagulation pathways during clot formation in an individual patient may be critical to select patients for DPI strategies that would strike a balance between anti-ischemic effects and risk of bleeding. In this line, we discuss the importance of the thrombin pathway, and the currently available studies of DPI in patients with ACS who are not required to be treated with anticoagulant therapy, such as patients without atrial fibrillation, venous thrombosis, mechanical valves, ventricular thrombus, or peripheral artery disease.

ROLE OF THROMBIN PATHWAY IN ACS: CURRENT CONCEPT

In conjunction with platelet activation and aggregation following binding of platelets to exposed subendothelial matrix, tissue factor (TF) exposed at the site of vascular injury binds to the circulating FVIIa and forms the extrinsic

tenase complex, TF-FVIIa. TF-FVIIa complex activates FX to FXa. FXa binds to FVa to form prothrombinase complex that converts small quantities of prothrombin to thrombin. The propagation of thrombus formation initiated by the extrinsic pathway with TF-FVIIa complex (extrinsic tenase) may be limited once the thrombus enlarges and extends beyond the TF source at the site of injury (exposed endothelium). At the same time, antithrombotic agents released by the healthy vessel wall such as ectoADPase, prostaglandin I₂, and nitric oxide, limit the propagation of platelet activation and coagulation. High levels of TF exposure at the site of vascular injury in the adventitia during normal hemostasis initiates explosive generation of thrombin. It has been hypothesized that the involvement of the intrinsic pathway (FXIIa, FXIa and FIXa) is of minimal importance during normal hemostasis [14, 15].

In the intrinsic pathway of coagulation, following exposure to a negatively charged surface, FXII undergoes autoactivation to FXIIa (contact activation). Negatively charged surfaces include activated platelets, subendothelial collagen, implanted devices, or naturally occurring polyanions such as neutrophil extracellular traps, inorganic polyphosphate released from activated platelets, or deoxyribonucleic acid or ribonucleic acid released from dead or dying cells. FXIIa activates FXI to FXIa, and FXIa subsequently converts FIX to IXa that binds to FVIIIa. FVII and FXI can be activated by a small amount of thrombin at the site of vascular injury in a feedback activation pathway. These pathways can bypass the FXIIa-mediated activation. In addition, TF-FVIIa complex activates FIX to FIXa on the surface of platelets in the "cross-over pathway". The FIXa + FVIIIa (intrinsic tenase) complex converts FXa that subsequently binds to FVa. The FXa + FVa complex converts a large amount of prothrombin to thrombin in the common propagation pathway of coagulation (Figure 1). It has been hypothesized that FXIa and FXIIa are essential for the amplification of thrombin generation beyond the initial burst of thrombin generated by TF and for the growth and stabilization of pathological clot during pathological conditions, but not for normal hemostasis [14, 15].

In addition to its role in the amplification of thrombin generation, factor Xa has been shown to directly activate protease-activated receptor (PAR)-2 signaling, or indirectly activate protease activated receptor-1 *via* thrombin generation with resultant release of proinflammatory cytokines and the expression of cell adhesion molecules in the atherosclerosis process [16]. In this scenario, potential targets to inhibit coagulation with oral agents include direct thrombin inhibitors (dabigatran), FXa inhibitors (rivaroxaban, apixaban, edoxaban), FXIa inhibitors (asundexian and milvexian), and FXIIa inhibitors.

ELEVATED THROMBIN GENERATION IN PATIENTS WITH ACS

Thrombin is a potent platelet agonist; it converts fibrinogen to fibrin and is essential for angiogenesis and wound

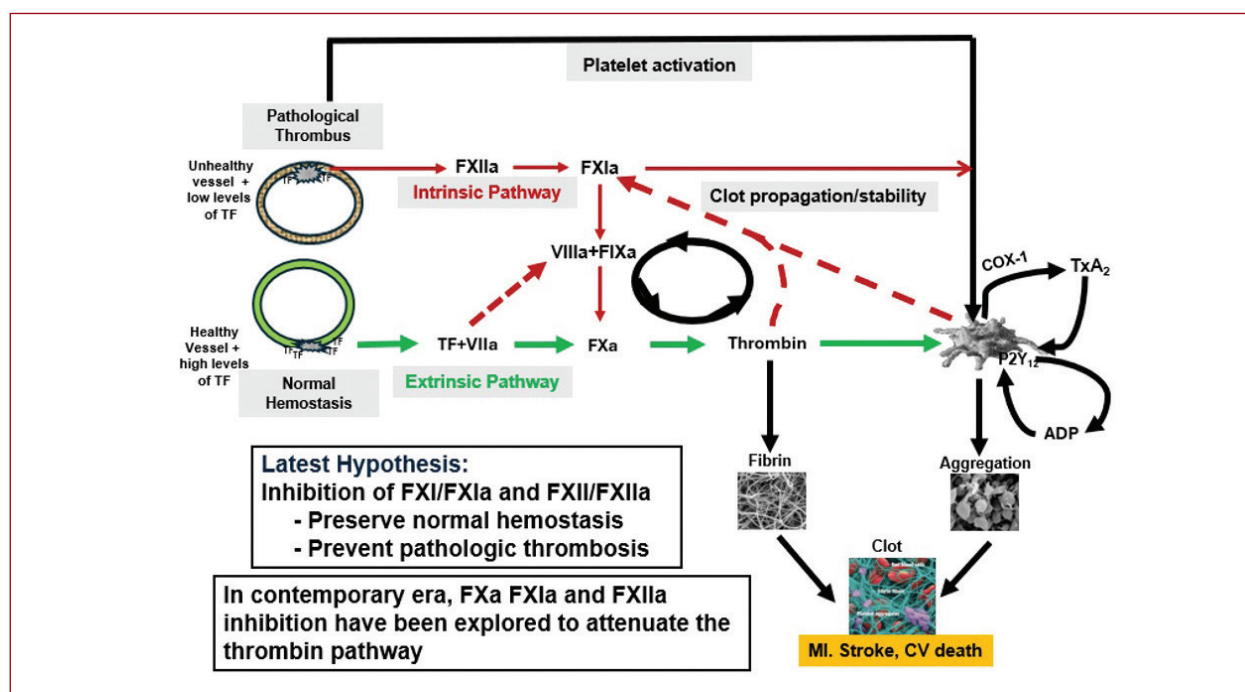


Figure 1. Role of thrombin pathway in acute coronary syndrome (ACS)

Abbreviations: COX-1, cyclooxygenase-1; CV, cardiovascular; MI, myocardial infarction; TF, tissue factor; TxA₂, thromboxane A₂

healing. Characteristics of coronary artery thrombi collected during thrombectomy at different times from patients with MI were evaluated using high-resolution scanning electron microscopy. Fibrin was the main component (56%) of the clot, followed by platelets (17%), erythrocytes (11%), cholesterol crystals (5%), and leukocytes (~1.5%). The time between the onset of symptoms and thrombus aspiration was strongly associated with thrombus composition and patient clinical history. There was a two-fold increase in fibrin content and a 50% reduction in platelets for every ischemic hour [17]. In a prospective multicenter cohort study of patients with ACS, persistently elevated thrombin generation as assessed by plasma prothrombin fragment 1 + 2 levels (an index of *in vivo* thrombin generation) was observed. Both high and low levels of thrombin were associated with an increased risk of an unfavorable 29-month outcome [18]. Similarly, in patients with unstable angina and MI, elevated coagulation activity was observed during the acute phase, which persisted for over 6 months [169]. Elevated thrombin generation has been reported in patients with ACS, as compared to patients with stable coronary artery disease or healthy controls [20]. Similarly, heightened thrombin generation was reported in patients after acute MI, which remained elevated during 6 months of follow-up [21].

These studies highlight the fact that patients with ACS are “clot formers” with heightened thrombin generation after MI, which remains elevated during long-term follow-up. Therefore, in addition to optimal inhibition of platelets, inhibition of thrombin may be needed to optimally attenuate subsequent thrombus formation and ischemic event

occurrences. However, studies indicate that uniform potent inhibition of both platelet and coagulation pathways leads to an unacceptable risk for major bleeding that is in turn associated with a high mortality risk [22]. Therefore, uniform use of DPI is not advisable, and identifying patients with a high risk for ischemia without an added risk for bleeding is critical. Currently, guidelines recommend bleeding risk scores to select patients to avoid excess bleeding risk for treatment with DPIs [10, 11]. The identification of a patient with a heightened “thrombin pathway” may be a critical component of personalized therapy with DPI.

HOW CAN WE IDENTIFY THE PATIENT WITH A HEIGHTENED “THROMBIN PATHWAY”?

Thromboelastography (TEG), an *ex vivo* viscoelastic hemostatic assay, provides information on dynamic changes in clot characteristics from the initiation of clot formation to platelet-fibrin clot generation, and clot stability. In addition to information on the contribution of platelets and fibrin to clot formation, TEG can provide information on thrombin generation, the response to antiplatelet and anticoagulant agents, and fibrinolysis [23]. In a seminal prospective study of patients undergoing PCI and treated with clopidogrel and aspirin, we demonstrated the relationship between laboratory measurements using TEG (time to initial clot formation [R-value, an assessment of the enzymatic phase of coagulation] and platelet-fibrin clot strength measured before discharge) and 6-month cardiovascular (CV) death, MI, stroke, and unstable angina. Blueprinting of the thrombogenicity profile in this study showed that 85% of patients who developed post-PCI ischemic events were hypercoag-

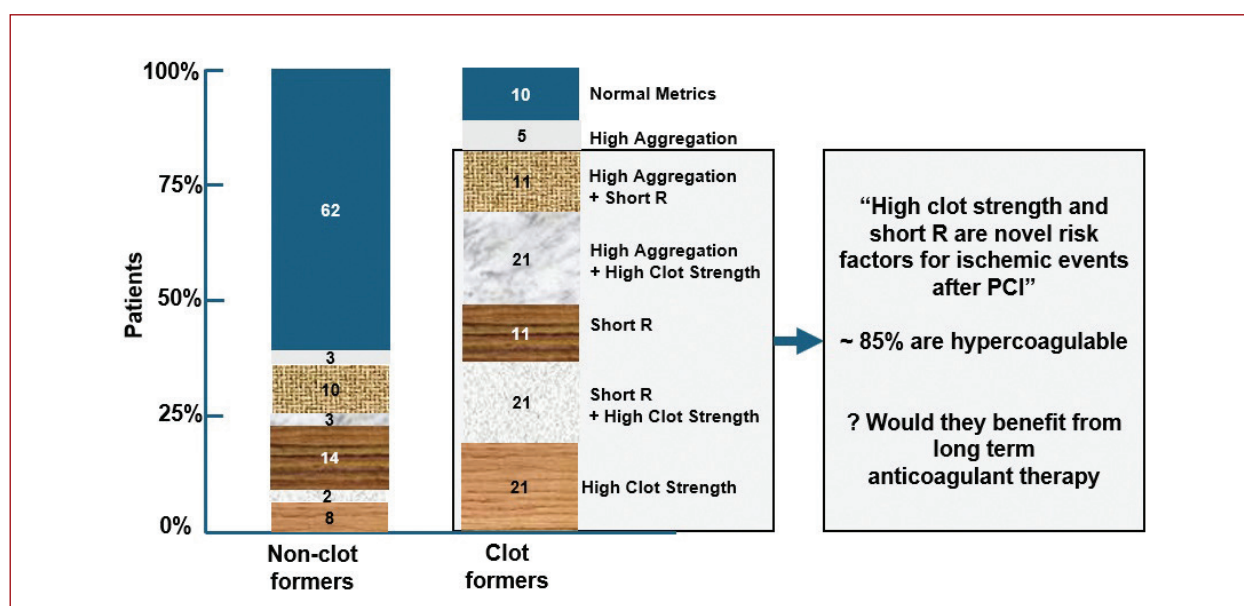


Figure 2. Distribution of patients

Abbreviation: PCI, percutaneous coronary intervention

ulable, as indicated by a short R-value (<3.9 minutes) and/or high platelet fibrin clot strength (>72 mm), as compared to 27% of patients without post-PCI ischemic events (Figure 2). At that time, we postulated that these patients with hypercoagulability will benefit from long-term anticoagulation therapy in addition to antiplatelet therapy [24].

Further studies from our group demonstrated that high platelet-fibrin clot strength is associated with high levels of inflammation markers such as fibrinogen, von Willebrand factor, and C-reactive protein [25, 26]. In a recent study conducted in South Korea involving 2705 coronary artery disease patients, hypercoagulability (clot strength ≥ 68 mm) was associated with high risk for 4-year MACE (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.26–2.30; $P < 0.001$), and hypercoagulability was more pronounced in patients with STEMI [27]. Similarly, in another study of 116 patients with ACS, hypercoagulability was more pronounced in patients with coronary microvascular dysfunction (microcirculatory resistance of >40 U using an invasive physiologic test) and risk stratification with coronary microvascular dysfunction and hypercoagulability was synergistic in predicting 3-year MACE (odds ratio of 5.58) [28]. In a recent study conducted at our center, the prevalence of hypercoagulability (clot strength ≥ 67 mm) was significantly higher (80%–100%) in ACS patients with prior MI or stroke as compared to patients without MI or stroke (33%–56%) [29]. The presence of high recurrent ischemic risk in contemporary translational research studies and earlier studies of potent P2Y₁₂ receptor inhibitors indicates a major unmet need with potent platelet inhibition in ACS patients and provides a rationale for treatment with DPLs.

NON-PERSONALIZED FULL-DOSE ORAL ANTICOAGULATION ADDED TO ANTIPLATELET THERAPY IN THE ACS PATIENT HAS CLINICALLY FAILED

With the development of safer and direct oral anticoagulants as compared to earlier warfarin, numerous clinical trials have been undertaken in ACS patients without an indication for oral anticoagulation and treated with a DOAC agent added to an antiplatelet agent (preferably aspirin).

TARGETING THROMBIN DIRECTLY

In a phase 2 trial of ACS patients after an average of 7.5 days of an index event, dabigatran (50–150 mg twice daily) added to DAPT vs. DAPT alone reduced coagulation activity but was associated with a dose-dependent increase in bleeding [30].

TARGETING FXa

Two clinical trials studied the benefit of adding rivaroxaban to antiplatelet therapy in patients with ACS. In the phase II Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome — Thrombolysis in Myocardial Infarction 46 (ATLAS ACS-TIMI 46) trial, 3491 patients who were stabilized after ACS (1–7 days after hospital admission) were treated with escalating doses of rivaroxaban (5–20 mg daily) on top of aspirin vs. aspirin plus a thienopyridine (mainly clopidogrel). During the 6-month follow-up period, rivaroxaban was associated with a significant reduction in death, MI or stroke (HR, 0.69; $P = 0.0270$), along with an elevated risk of clinically significant bleeding ($P < 0.0001$) [8]. Based on the graded increase in bleeding across doses of rivaroxaban

Table 1. Outcomes in aspirin + 2.5 mg bid rivaroxaban vs. aspirin alone groups in the COMPASS trial

Outcome	COMPASS —overall (n = 27 395)	COMPASS — CAD (n = 24 824)	COMPASS — PAD (n = 7470)
Major adverse cardiovascular events	4.1% vs. 5.4% HR, 0.76 95% CI, 0.66–0.86 <i>P</i> < 0.001	4% vs. 6% HR, 0.74 95% CI, 0.78–1.02 <i>P</i> < 0.0001	5% vs. 7% HR, 0.72 95% CI, 0.57–0.90 <i>P</i> < 0.001
Myocardial infarction	1.9% vs. 2.2% HR, 0.86 95% CI, 0.70–1.05 <i>P</i> = 0.14	2% vs. 2% HR, 0.86 95% CI, 0.70–1.05 <i>P</i> = 0.15	ALI, 1% vs. 1% HR, 0.56 95% CI, 0.32–0.99 <i>P</i> = 0.042
Stroke	0.9% vs. 1.6% HR, 0.58 95% CI, 0.44–0.76 <i>P</i> < 0.001	1% vs. 2% HR, 0.56 95% CI, 0.42–0.75 <i>P</i> < 0.0001	MALE, 1% vs. 2% HR, 0.54 95% CI, 0.35–0.84 <i>P</i> = 0.0054
Cardiovascular death	1.7% vs. 2.2% HR, 0.78 95% CI, 0.64–0.96 <i>P</i> = 0.02	2% vs. 2% HR, 0.75 95% CI, 0.60–0.93 <i>P</i> = 0.01	MALE + MA, 1% vs. 2% HR, 0.54 95% CI, 0.35–0.82 <i>P</i> = 0.0037
All cause death	3.4% vs. 4.1% HR, 0.82 95% CI, 0.71–0.96 <i>P</i> = 0.01	3% vs. 4% HR, 0.77 95% CI, 0.65–0.90 <i>P</i> = 0.0012	5% vs. 6% HR, 0.91 95% CI, 0.72–1.16 —
Major bleeding	3.1% vs. 1.9% HR, 1.70 95% CI, 1.40–2.05 <i>P</i> < 0.001	3% vs. 2% HR, 1.66 95% CI, 1.37–2.03 <i>P</i> < 0.0001	3% vs. 2% HR, 1.61 95% CI, 1.12–2.31 <i>P</i> < 0.0089

Abbreviations: ALI, acute limb ischemia; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MA, major amputation; MALE, major adverse limb events; PAD, peripheral artery disease

and with the efficacy associated with lower doses, 2.5 mg and 5 mg bid rivaroxaban were studied in the phase III ATLAS ACS-TIMI 51 trial. In this trial, 15 526 patients with a recent ACS (3.2 to 6.0 days) received 2.5 mg or 5 mg bid rivaroxaban or placebo on top of aspirin plus clopidogrel for a mean of 13 months. The primary efficacy endpoint of the composite of CV death, MI, or stroke was lower with the 2.5 mg b.i.d. rivaroxaban dose (9.1% vs. 10.7%; *P* = 0.02) and the 5 mg dose b.i.d. rivaroxaban (8.8% vs. 10.7%; *P* = 0.03). In addition, 2.5 mg bid rivaroxaban was associated with a reduction in the rate of CV death (2.7% vs. 4.1%; *P* = 0.002) and any-cause death (2.9% vs. 4.5 %; *P* = 0.002), which was not observed with a 5 mg dose b.i.d. The 2.5 mg b.i.d. rivaroxaban dose was associated with fewer fatal bleeding events than the 5 mg b.i.d. dose (0.1% vs. 0.4%; *P* = 0.04) [9]. Based on the results of ATLAS trials, the European medical agency recommended 2.5 mg rivaroxaban b.i.d. on top of aspirin and clopidogrel in patients with stabilized ACS, but the same recommendation was not included in the European Society of Cardiology guidelines [31].

The FXa inhibitor apixaban was studied in patients with recent ACS (≤7 days). In this trial of 7392 patients, apixaban 5 mg b.i.d. vs. placebo on top of standard DAPT was associated with a similar rate of MACE (HR, 0.95; 95% CI, 0.80–1.11; *P* = 0.51) and an elevated risk of TIMI major bleeding (HR, 2.59; 95% CI, 1.50–4.46; *P* = 0.001), which resulted in the trial being prematurely terminated [7]. Based on the results of the ATLAS trials, a very low dose (2.5 mg b.i.d.) was chosen in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. In this study, patients with stable atherosclerotic vascular disease were treated with rivaroxaban (2.5 mg b.i.d.) plus aspirin (100 mg

q.d.), rivaroxaban (5 mg b.i.d.), or aspirin (100 mg q.d.). There was a 24% reduction in MACE (4.1% vs. 5.4%; HR, 0.76; 95% CI, 0.66–0.86; *P* < 0.001), a 49% reduction in ischemic stroke (HR, 0.51; 95% CI, 0.38–0.58; *P* < 0.001), a 42% reduction in overall stroke (HR, 0.58; 95% CI, 0.44–0.76; *P* < 0.00), an 18% reduction in all-cause death (HR, 0.82; 95% CI, 0.71–0.96; *P* = 0.01), and 22% reduction in CV death (HR, 0.78; 95% CI, 0.64–0.96; *P* = 0.02) with very-low-dose rivaroxaban plus acetylsalicylic acid vs. aspirin alone, whereas no MACE reduction was associated with rivaroxaban 5 mg b.i.d. alone (4.9% vs. 5.4%; HR, 0.90; 95% CI, 0.79–1.03; *P* = 0.12). The rates of MI were similar among all arms. With respect to bleeding, very-low-dose rivaroxaban plus aspirin vs. aspirin alone was associated with a higher rate of major bleeding (HR, 1.70; 95% CI, 1.40–2.05; *P* < 0.001), which was driven by more gastrointestinal bleeding events (HR, 2.15; 95% CI 1.60–2.89; *P* < 0.001) [32]. The relative values for the important outcomes in patients with stable atherosclerotic vascular disease, stable coronary artery disease, and peripheral artery disease are presented in Table 1 [33, 34].

In a net clinical benefit analysis that was used by guidelines to recommend rivaroxaban, 2.5 mg b.i.d. rivaroxaban plus aspirin vs. aspirin alone was associated with a 20% reduction in MACE that was mainly driven by a 42% reduction in stroke (*P* < 0.001) and 22% reduction in CV death (*P* = 0.02) but with a statistically non-significant 49% and 37% increase in fatal bleeding and symptomatic bleeding into a critical organ, respectively. The net clinical benefit favored 2.5 mg rivaroxaban plus aspirin therapy with a 20% reduction (*P* = 0.005) [35]. The latter analysis did not include the modified International Society of Thrombosis and Hemostasis bleeding variable from the main

study that included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization. The net benefit was more pronounced in selected high-risk subgroups such as patients with polyvascular disease (≥ 2 vascular beds affected with atherosclerosis), impaired renal function, heart failure, and/or diabetes mellitus.

ANTITHROMBOTIC SYNERGY BETWEEN THROMBIN AND CYCLOOXYGENASE-1 PATHWAYS INHIBITION

One of the important take-home messages of the COM-PASS trial is that MACE reduction was observed in patients treated with 2.5 mg rivaroxaban plus aspirin but not with 5 mg rivaroxaban alone, indicating that direct thrombin inhibitor is more effective than anticoagulation or aspirin alone. In other words, very low dose DOAC may have synergistic anti-ischemic benefit when added to aspirin. In this line, noncanonical effects of aspirin should be discussed.

The canonical effect of aspirin has been attributed to specific acetylation of a serine residue at position 530 in the platelet cyclooxygenase (COX)-1 enzyme's active site and subsequent inhibition of the generation of thromboxane A_2 from arachidonic acid and arachidonic acid-induced platelet aggregation. In addition, it has been suggested that aspirin can nonspecifically acetylate other proteins such as fibrinogen or fibrin, which results in the increasing susceptibility of fibrin clots to lysis [36, 37]. In addition, the inhibitory effect of aspirin on thrombin generation and attenuation of FXIII activation has been demonstrated [38, 39]. In addition to inhibiting COX-1-specific arachidonic acid-induced platelet aggregation, aspirin has been shown to inhibit platelet aggregation induced by non-COX-1 pathways such as adenosine diphosphate- and collagen-induced platelet aggregation in a dose-dependent fashion [40]. Similarly, an *in vitro* study showed that rivaroxaban can accelerate fibrinolysis by inhibiting thrombin generation [41]. In another *in vitro* study with human platelet-rich plasma, inhibition of thrombin generation was enhanced when ticagrelor and ticagrelor plus aspirin were added to rivaroxaban. Also, low doses of rivaroxaban enhanced the antithrombotic effect of aspirin or aspirin plus clopidogrel in an arteriovenous shunt model involving male Wistar rats [42].

These observations support the synergistic anti-ischemic effects of rivaroxaban and aspirin in the COMPASS trial. However, in a small, randomized study of patients with coronary artery disease with or without peripheral arterial disease on long-term aspirin therapy, adding rivaroxaban 2.5 mg BID for 12 weeks did not show any influence on platelet aggregation, platelet fibrin clot strength, fibrinogen, or inflammation markers but reduced D-dimer levels. The latter results suggest a more marginal antithrombotic effect of 2.5 mg b.i.d. rivaroxaban on thrombin generation when added to aspirin therapy [43, 44]. In a recent *ex vivo* study of patients with peripheral

artery disease, treatment with 2.5 mg b.i.d. rivaroxaban and 75 mg aspirin q.d. was associated with lower thrombin generation and D-dimer levels, but there was no significant difference in fibrin clot network density, its lysability, and levels of fibrinolysis inhibitors as compared to baseline [45].

FXI AND FXIa INHIBITORS IN ACS

The contact system, particularly FXI activation, may be more important for clot stabilization and ischemic event occurrences and less important during normal hemostasis. Furthermore, patients with hemophilia C (congenital FXI deficiency) exhibit mild bleeding events, whereas patients with elevated FXI levels exhibit a higher risk for ischemic events [14]. The latest hypothesis is that the FXIa inhibitors can preserve normal hemostasis and prevent pathological thrombosis [46]. There are many classes of FXI/FXIa inhibitors — antisense oligonucleotides, monoclonal antibodies, small synthetic molecules, natural peptides, and aptamers. Most studies of FXI/FXIa inhibitors focus on the prevention of thromboembolic events. In a phase 2 trial of patients with recent acute MI on dual antiplatelet therapy (mainly ticagrelor or prasugrel plus aspirin), asundexian 10, 20, or 50 mg once daily was associated with dose-dependent inhibition of FXIa activity, no significant increase in bleeding, and lower risk for ischemia [47]. In the phase 3 Librexia ACS trial of 16 000 patients within 7 days of onset of ACS who had undergone cardiac catheterization with percutaneous coronary intervention or were being managed conservatively with or without catheterization (NCT0574957), the efficacy and safety of oral milvexian (25 mg twice daily) as an adjunct to standard-of-care antiplatelet therapy vs. placebo was studied. The primary outcome was MACE with follow-up until 875 events, secondary outcomes included combination of MACE, major adverse limb events, and venous thromboembolic events and the primary safety end point was Bleeding Academic Research Consortium 3c or 5 bleeding [48]. On November 14, 2025, it was announced that a decision had been made to stop the Phase 3 Librexia ACS trial after a preplanned interim analysis by the Independent Data Monitoring Committee determined the trial was unlikely to meet the primary efficacy endpoint. However, no safety concerns related to milvexian were identified, and the safety profile was consistent with previously reported studies of milvexian. Despite these findings, milvexian is currently being studied in stroke prevention trials [49].

FXIIa INHIBITORS

Similarly to FXI deficiency, bleeding is rare in subjects with inherited deficiency of FXII even in patients undergoing surgery, and these subjects exhibit longer activated partial thromboplastin clotting time with no influence on prothrombin time [50]. FXII knockout mice have been shown to exhibit protection against chemically and mechanically induced arterial and venous thromboses in addition to having normal bleeding times [51]. These finding stimulated

the development of inhibitors of FXII to prevent thrombosis with less effect on bleeding. In mouse models, the inhibition of FXIIa with a monoclonal antibody was shown to reduce the severity of abdominal aortic aneurysms and the progression of atherosclerosis and to stabilize vulnerable plaques. By direct binding to the N-terminus of fibrin(ogen), FXIIa may modulate fibrin clot structure independently of thrombin generation [52]. However, no FXII inhibitors are being explored currently in patients with ACS. It should be noted that FXI and FVIII can be directly activated by thrombin, bypassing the FXIIa-mediated activation. Therefore, FXIIa inhibitors may play a role in inhibiting clot formation in cases of device- or surface-related clot formation.

CONCLUSIONS

We have learned in the last 2 decades that the benefit of potent P2Y₁₂ inhibitors in the ACS patient is limited. There are persistent high event rates even with marked platelet inhibition. Very low dose FXa inhibitor added to aspirin in chronic atherosclerotic vascular disease is approved, but bleeding is high. The observation of no benefit in reducing MI in this population (chronic coronary disease patients) contrasts with the favorable results of administration within days of ACS, as observed in the ATLAS Study.

Finally, 85% patients who develop ischemic events within 6 months after PCI are hypercoagulable by at least one TEG metric at the time of PCI. Moreover, patients with prior MI or stroke undergoing intervention have a very high prevalence of hypercoagulability. Identification of the hypercoagulable ACS patient with a biomarker (such as clot strength or time to clot formation measured by viscoelastic testing) may facilitate individualized thrombin pathway inhibition. Despite the appealing theory behind the utility of FXIa inhibition to prevent pathologic thrombosis whilst sparing hemostasis, the results of the latest trial of milvexian in ACS was stopped due to futility. The reasons behind this disappointing result may be related to underdosing. More information is needed; however, failed theory may also be the reason. Further understanding of the mechanisms underlying the complex processes involved in recurrent ischemic and bleeding events in the ACS patient is required. "Blueprinting" platelet- and coagulation-related pathways with viscoelastic testing may advance personalized antithrombotic therapy.

Article information

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tection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient. PAG was an expert witness in a lawsuit associated with Plavix.

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